

Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Claims 50-61 are pending in the application, with claim 50 being the independent claim. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated May 11, 2009, the Examiner has made two rejections of the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. The Rejection Under 35 U.S.C. § 112, Second Paragraph Is Traversed

In section 6 of the Office Action at page 2, the Examiner has rejected claims 50-61 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner contends that "[t]he metes and bounds of the claim are not clear and the instant specification does not define the meaning of the term 'substantially' as would be applicable to the 'tetrameric form of uricase.'" *See* Office Action at page 2. Applicants respectfully disagree for the reasons discussed below.

First, Applicants note that the M.P.E.P. itself asserts the term "substantially" can be commonly used in conjunction with another term to describe a particular characteristic of a claimed invention, and courts have found that the term "substantially" is definite when viewed in light of general guidelines contained in the specification and level of skill in the art. *See* M.P.E.P. § 2173.05(b)(D).

Furthermore, the use of relative terminology does not render a claim indefinite so long as a person of ordinary skill in the art would be apprised of the scope of an invention. *See Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819 (Fed. Cir. 1988) (The court held that the limitation "which produces substantially equal E and H plane illumination patterns" was definite because one of ordinary skill in the art would know what was meant by "substantially equal.").

In addition, the Federal Circuit has specifically held that recitation of the term "substantially" in a claim does not *per se* render a claim indefinite.

The question is not whether the word "substantially" has a fixed meaning as applied to [a particular technology], but how the phrase would be understood by persons experienced in this field . . . upon reading the patent documents . . .

Expressions such as "substantially" are used in patent documents when warranted by the nature of the invention, in order to accommodate the minor variations that may be appropriate to secure the invention. Such usage may well satisfy the charge to "particularly point out and distinctly claim" the invention, 35 U.S.C. § 112, and indeed may be necessary in order to provide the inventor with the benefit of his invention . . .

It is well established that when the term "substantially" serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite.

Verve, LLC v. Crane Cams, Inc., 311 F.3d 1116, 1119-20 (Fed. Cir. 2002).

In the present case, Applicants respectfully point out that the specification provides sufficient written description such that the term "substantially" is definite. Specifically the specification states that

Other embodiments of the present invention are a method for isolating a tetrameric form of uricase from a solution containing multiple forms of uricase and the product of that method. . . . In

one aspect of this embodiment, the purified tetrameric uricase may contain less than about 10% uricase aggregates.

[S]ubstantially all aggregates of the tetrameric form of the enzyme may be removed by ion-exchange or size-exclusion chromatography at a pH between about 9 and 10.5, preferably 10.2, prior to PEG conjugation of the resulting *substantially tetrameric* preparation of uricase.

See specification at page 10, lines 15-17 and 27-29 and page 16, lines 23-26 (emphasis added). Therefore, Applicants respectfully submit that when viewed with reference to the present specification, the term "substantially" would be readily understood by one of ordinary skill in the art.

Furthermore, the Examiner has acknowledged in the Office Action at page 4 that the ordinary meaning of the term "substantially" is "to a great extent or degree." Thus, the Examiner concludes that the phrase "wherein said uricase is in a substantially tetrameric form" encompasses uricase which is "to a greater extent or degree in tetrameric form." The Examiner further states that "[l]ess than 10% of said uricase is in [a] non-tetrameric aggregated form is interpreted to mean - that 0-10% of said uricase could also be non-tetrameric aggregated" uricase. *See* Office Action at page 4. Applicants agree with the Examiner with respect to the interpretation of the term "substantially." Thus, based on the Examiner's ordinary meaning of the term "substantially" and the additional claim elements of claim 50, Applicants respectfully assert that one of ordinary skill in the art would clearly understand that the uricase is predominantly in the tetrameric form except for less than 10% of the uricase that is in a non-tetrameric aggregated form.

Finally, claim 50 recites "wherein said uricase is in a substantially tetrameric form, and wherein less than 10% of said uricase is in a non-tetrameric aggregated form." Thus, Applicants respectfully assert based on this claim language alone one of ordinary skill in the

art would clearly understand that the uricase is predominantly in the tetrameric form except for less than 10% of the uricase that is in a non-tetrameric aggregated form. Interpreting "substantially" any other way would result in the elimination of the "less than 10% of said uricase is in a non-tetrameric aggregated form" element from the present claims. Therefore, based on the disclosure in the specification, the Examiner's statements and claim 50 itself, Applicants respectfully contend that the metes and bounds of the claims are clear. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

IV. The Rejection Under 35 U.S.C. § 102(b) Is Traversed

In section 7 of the Office Action at pages 3-6, the Examiner has maintained the rejection of claims 50-53 under 35 U.S.C. § 102(b) as allegedly being anticipated by Lee *et al.*, *Science* 239: 1288-1291 (1988) (hereinafter "Lee"). Applicants respectfully traverse this rejection.

The Examiner contends that Lee allegedly discloses porcine uricase that is 'tetrameric and is substantially pure.' *See* Office Action at page 3. The Examiner further contends that use of the term "substantially" allegedly "encompass[es] a range of uricase or perhaps a greater extent or degree in tetrameric form, with no limit to the range in general and especially with no upper limit." The Examiner concludes that "any prior art uricase preparation that contains such an undefined range of the uricase in tetrameric form is encompassed" by the present claims. *See* Office Action at page 4. Applicants respectfully disagree with the Examiner.

First, as discussed above, claim 50 is directed to "an isolated tetrameric mammalian uricase, wherein said uricase is in a substantially tetrameric form, and wherein less than 10%

of said uricase is in a non-tetrameric aggregated form." Thus, by *definition* the presently claimed tetrameric uricase preparations must contain *greater than* 90% of the uricase in the tetrameric form.

Furthermore, Applicants again assert that Lee does not *expressly* disclose preparations of isolated tetrameric uricase in which the uricase is in a substantially tetrameric form, and wherein less than 10% is in a non-tetrameric aggregated form, as recited by the claims. Correspondingly, Lee does not disclose uricase preparations having *greater than* 90% of the uricase in the tetrameric form. The disclosure of Lee is limited to the disclosure of three uricase preparations; however, *none* of the uricase preparations disclosed in Lee is a uricase preparation in a substantially tetrameric form, wherein less than 10% is in a non-tetrameric aggregated form. First, Lee discloses a commercial preparation of porcine liver uricase from Sigma. Second, Lee also discloses a natural preparation of murine liver uricase. Applicants respectfully assert that Lee does not indicate *what* form these two uricase preparations were in, let alone that these preparations were in a substantially tetrameric form, wherein less than 10% of the uricase was in a non-tetrameric aggregated form. Moreover, as discussed in more detail below, at least the first of these preparations contains significantly more than 10% of the uricase in a non-tetrameric aggregated form. Third, Lee discloses a uricase preparation where the commercial porcine uricase and natural murine liver uricase have been "purified to homogeneity" by SDS-PAGE. *See* Lee at pages 1289 and 1291. However, the "homogeneous" uricase preparations of Lee do *not* contain 100% uricase tetramers -- instead they contain isolated monomers, formed from an undisclosed mixture containing aggregates of isolated uricase by the SDS-PAGE process used in Lee.¹ Thus, as one of ordinary skill

¹ As one of ordinary skill would be readily aware, the use of sodium dodecyl sulfate (SDS) in the polyacrylamide gel electrophoresis (PAGE) methods in Lee would result in complete disaggregation of any and

would readily appreciate, Lee does not expressly disclose any preparation of isolated uricase in which the uricase is in a substantially tetrameric form and less than 10% is in a non-tetrameric aggregated form.

Despite the Examiner's repeated assertions to the contrary, Applicants note that the preparations of uricase obtained by Lee for use in the preparative or analytical SDS-PAGE disclosed in that reference are not in the native tetrameric form. This fact is supported by Example 1 in the present specification which discloses that the commercial preparation of porcine liver uricase used in Lee (and also used as a starting material by the inventors of the present application) had to be purified by the methods described in the present application in order to obtain a preparation of uricase that is in a substantially tetrameric form, and wherein less than 10% of the uricase is in a non-tetrameric aggregated form. *See* specification at page 16, lines 23-26. The present specification further discloses that natural and recombinant uricases isolated from bacteria, fungi, mammals and plants require purification by the methods described in the present specification in order to obtain an isolated tetrameric uricase preparation in which the uricase is in a substantially tetrameric form, and wherein less than 10% of the uricase is in a non-tetrameric aggregated form. *See* specification at Examples 4-10. Thus, the commercial preparation of porcine liver uricase and the natural preparation of murine liver uricase disclosed in Lee clearly would not have been expected to contain substantially tetrameric uricase, wherein less than 10% of the uricase is in a non-tetrameric aggregated form.

With regard to the Examiner's statements that "murine urate oxidase was purified to homogeneity by using the method of Conley (1979)" and "Conley (1979) teaches purification

every multimeric form of uricase into the monomeric subunits -- hence this method produces the same result (*i.e.*, only the monomeric subunit form is observed on the gel) no matter what the state of aggregation of the

of uricase from mammalian tissue by precipitation under certain dialysis conditions," (*see* Office Action at page 4) Applicants respectfully assert that the Examiner has misconstrued the teaching of Conley. As discussed above, the method of Lee (as described in Conley) does not and would not provide a "homogenous" tetrameric uricase preparation. Although Conley states that the "purification" of uricase is based on the precipitation of mammalian uricase under certain dialysis conditions, Applicants respectfully point out to the Examiner that precipitation of uricase is nothing more than formation of uricase aggregates, including large aggregates of uricase, that are large enough to separate themselves from the solution under the force of gravity. This technique would not have led to the purification of a "homogenous" tetrameric uricase preparation; instead, this precipitation technique would merely "purify" uricase from other, non-uricase proteins in the preparation.

Furthermore, as discussed in Conley, the "homogeneity" (*i.e.*, purification of uricase from other non-uricase contaminants) of the preparation is determined by using polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate. *See* Conley at page 201, lines 3-5. As discussed above, dissolving uricase aggregates in the anionic detergent sodium dodecyl sulfate (SDS) dissociates the uricase into monomeric subunits, no matter what the state of aggregation of the uricase. Therefore, in contrast to the methods of the present application wherein *tetrameric* uricase is isolated, the method of Conley (and therefore Lee) did not produce a preparation of isolated uricase in which the uricase is in a substantially tetrameric form and less than 10% is in a non-tetrameric aggregated form – instead, the methods of Conley (and therefore Lee) produced preparations in which all (or, at worst, nearly all) of the uricase was in a monomeric form.

uricase polypeptides applied to the gel -- tetramers, octamers, or otherwise.

This conclusion is further supported by the data presented in the Second Declaration Under 37 C.F.R. § 1.132 by Merry R. Sherman, Ph.D., filed September 18, 2007. These data clearly show that the amount of non-tetrameric aggregated uricase that is present in the commercial preparation of porcine liver uricase used both in Lee and as a starting material in Example 1 of the present application was significantly higher than the "less than 10%" required by the present claims. *See* paragraph 7 and Figure 3 of the second Sherman Declaration. As is shown in Figure 3, and as stated by Dr. Sherman at paragraph 7, the Sigma porcine liver uricase (U3250) contained 21% octamer and 17% aggregates larger than octamer (*i.e.*, at least 38% of the uricase was in a non-tetrameric aggregated form) prior to purification by the methods described in the present specification. Furthermore, these data show that the amount of non-tetrameric aggregated uricase that is present in other isolated commercial, recombinant and natural uricase preparations was significantly higher than the "less than 10%" required by the present claims -- the Sigma porcine liver uricase (Catalog No. U3377) contained 11% octamer and 3% aggregates larger than octamer; the soybean uricase contained 22% octamer and 13% aggregates larger than octamer; and the *Candida utilis* uricase (Sigma Catalog No. U1878) contained 21% octamer and 19% aggregates larger than octamer, prior to purification by the methods described in the present application. *See* Figures 4 and 5 and paragraphs 8 and 10-11 of the second Sherman Declaration.

Indeed, as Dr. Sherman stated at paragraphs 10 and 16 of the second Sherman declaration and as Figures 1, 2 and 5 clearly show, preparations of uricase that contain less than 10% in a non-tetrameric aggregated form (such as the presently claimed uricase preparations) are obtainable only by using isolation methods such as those described in the present specification, which are not described in Lee. *See* Figures 1, 2, and 5 and paragraphs 10 and 16 of the second Sherman Declaration. Hence, as described in the present

specification, and as is clearly shown in the second Sherman Declaration, without specifically purifying the uricase preparations using methods such as those described in the present specification, the uricase preparations disclosed in Lee would not (and did not) contain substantially tetrameric uricase, wherein less than 10% of the uricase is in a non-tetrameric aggregated form. In fact, at best Lee discloses only two types of uricase preparations: (1) the starting material which, as discussed above, contains more than 10% of the uricase in a non-tetrameric aggregated form and (2) SDS-PAGE purified uricase which is all or nearly all monomeric. Thus, as one of ordinary skill in the art would readily appreciate, Lee does not expressly disclose an isolated tetrameric mammalian uricase having the characteristics recited in the present claims.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). As discussed above, Lee does not expressly or inherently disclose every element of the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b). In view of the foregoing remarks, Applicants respectfully assert that Lee does not anticipate claims 50-53. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Lee therefore are respectfully requested.

V. Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and

Reply dated August 11, 2009
Reply to Office Action of May 11, 2009

- 11 -

WILLIAMS *et al.*
Appl. No. 09/839,946

complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Shannon A. Carroll, Ph.D.
Attorney for Applicants
Registration No. 58,240

Date: August 11, 2009

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
1005528_4.DOC